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(19)

(54) TABLETING OF MICROCAPSULES

(71) We, HOECHST UK LIMITED, a British body corporate, of Hoechst House, Salisbury Road, Hounslow, Middlesex, TW4 6JH, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by it is to be performed, to be particularly described in and by the following statement:-

This invention relates to the tableting of brittle micro-capsules and other particles that have a brittle coat.

Microcapsules have many applications as the micro-encapsulated substance is protected from external influences and vice versa, for example, stability is increased and chances of undesirable reactions with other components in a mixture are substantially eliminated, unpleasant tastes and smells can be masked, and possibilities of irritation by noxious substances reduced. Micro-encapsulated substances are generally in the form of a flowable power, which is desirable for many purposes.

For other application, for example, in pharmaceutical use, it is advantageous to provide a substance in unit form to assist correct dosing. Although it is possible to provide a unit dose comprising granules or a powder in a sachet, this form of preparation is not entirely satisfactory, and the most common conventional unit dose forms of solid pharmaceutical preparations are tablets of all kinds, with pills, cachets, hard and soft gelatin capsules being less common for technical and commercial reasons. Other forms of preparations such as troches and wafers are rare nowadays.

Unit doses containing a known amount of a substance are alo useful in any situation where it is desired to produce a solution of known strength.

Attempts have been made to produce unit dose preparations comprising microcapsules. Gelatin capsules containing microcapsules have been prepared, but these are not suitable for pharmaceutical use when active substances are used in high doses because the capsules containing a suitable unit dose are too large to swallow. Attempts have been made to produce tablets comprising microcapsules, but again the problem is size: most microcapsules are very brittle, so large amounts of carriers for example, mixtures of lactose, microcrystalline cellulose and starch, have been found to be necessary to prevent rupture of the microcapsules on compression. This leads to tablets that are unacceptably large. In some cases, however, it has been found possible to produce a tablet of acceptable size comprising microcapsules, but in these cases, both involving acetylsalicyclic acid (aspirin), the size and shape of the acetylsalicyclic acid particles to be encapsulated must be carefully controlled and a low proportion of encapsulating material is used.

Polyethylene glycols have been used in small amounts as lubricants in conventional tablets, but they have not previously been proposed as carriers in attempts to tablet microcapsules. The present invention is based on the observation that even brittle microcapsules can be tableted successfully, *i.e.* the microcapsules retain their original properties, when a polyethylene glycol or another water-soluble, natural or synthetic wax is used as carrier.

The present invention provides a tablet or another solid, shaped article produced by compression which comprises a micro-encapsulated substance or a substance that has a brittle coating, and a water-soluble, natural or synthetic wax having a melting point of at least 30°C, preferably within the range of from 30 to 100°C, in an amount more than 2 % w/w and not more than 20% w/w, calculated on the microcapsules or substance having a brittle coating.

The term "brittle" is used herein to denote a microencapsulated substance or a coating that would crack if tableted or formed into a solid, shaped article by compression in the absence of the wax used in the present invention.

The invention also provides a process for preparing the tablet or other solid, shaped article of the invention, which comprises admixing the microencapsulated substance or substance having a brittle coating and the wax and, if desired, one or more carriers, and bringing the mixture into tablet form or the other desired solid form, or applying a solution of the wax in an organic solvent to the microencapsulated substance or substance having a brittle coating, if desired, before or after admixture with one or more carriers, and bringing the treated microencapsulated substance or substance having a brittle coating and any carriers present into tablet form or the other desired compressed solid form.

The mixture may be tableted by any method, for example, direction compression, wet granulation or dry granulation, and the resulting tablets may be subjected to any post-treatment, for example, coating, lacquering or sintering. Sintering has been found to be particularly advantageous, the sintering temperature preferably being about 10°C above the melting point of the wax used. (The term "tablet" as used in this paragraph and hereafter includes the other solid, shaped articles produced by compression, for example, pills, pellets and lozenges, and "tableting" includes the manufacture of such articles by compression).

Substances having brittle coatings, which can be tableted successfully according to the invention, are those coated other than by microencapsulation with for example an acrylic resin, ethylcellulose, nylon, glycerylmonostearate or beeswax.

Any water-soluble wax having the required melting point may be used in the tablets of the invention, for example, certain ethylene glycol derivatives, for example, polyethylene glycol, and certain stearates, for example, sodium stearate and polyoxyl 40 stearate. The preferred substance is polyethylene glycol, (called "PEG" hereafter), which is available commercially in various grades, the number assigned to a grade as in PEG 2000 indicating the average molecular weight of the polymer.

Polyethylene glycol has been used in the preparation of conventional tablets containing non-microencapsulated substances, but always in small amounts. We have found that when used in amounts of more than 2%, which is about the previous limit, and preferably 5 % or more, the effect on microcapsules is quite unexpected: The accompanying drawing shows the effect of increasing amounts of PEG 6000 on the release rate of KCl from tablets containing micro-encapsulated KCl, (KCl microcapsules being particularly brittle), which is to decrease the number of microcapsules ruptured during tableting. This effect occurs when the amount of PEG 6000 exceeds 2 %.

The amount of the wax used is therefore greater than 2 % w/w, calculated on the microcapsules or substance having a brittle coating, preferably more than 3 %, more preferably more than 5 %, and advantageously more than 6 %. Upper limits are determined by the size of the tablet, but in many cases amounts of wax in excess of 10 % produce little more effect on the protection of the microcapsules or substance having a brittle coating, so up to 10 % is the advantageous amount of wax in many cases. The upper limit of the wax is 20 %.

Some of the waxes are finely divided substances, for example, PEG 6000, which has a melting point within the range of from 55 to 60°C, is available as a powder, but most of the other grades of PEG having suitable melting points are in the form of waxy flakes. It is necessary to mill such a substance to a fine powder before use if it is to be admixed with the other components of the tablet. It is advisable to mill those grades having melting points in the lower end of the specified range in the presence of a cooling agent *e.g.* 50 % solid CO_2, to prevent melting. This also applies to any other suitable substance that is available in a form other than a powder and that is to be admixed with the other components rather than applied in the form of a solution.

As mentioned above, other carriers may be present, and it is advisable, especially when tableting microcapsules or other substances having a brittle coat to choose carriers that do not have sharp edges or corners. Microcrystalline cellulose, which has long, fibrous particles, is an example of a particularly suitable additional carrier. Other carriers which may be used are lactose, starches and sugars.

The microencapsulated substance or substance having a brittle coating may be any pharmacologically active substance, for example, a drug, a dietary supplement or a vitamin, especially any substance for which controlled release is required. This may be to enable release of the active substance in the duodenum or ileum rather than the stomach, or to ensure that the active substance, for example, acetylsalicyclic acid, is released at a controlled rate in the stomach to decrease the chance of damage to the gastric mucosa.

The method of this invention has been found to be particularly useful in the production of tablets comprising microencapsulated potassium chloride, these microcapsules being

particularly brittle. The potassium chloride tablets of the invention have disintegration times such that the microcapsules are readily released and dispersed in the stomach, thus avoiding a high local concentration of potassium chloride. Slow release microcapsules are especially used to reduce gastric irritation by causing release of the potassium chloride to occur slowly throughout the gastro-intestinal tract. The preferred wax for such tablets is a PEG, and the tablets are preferably sintered.

The tablets of the invention may comprise one active substance in microencapsulated or coated form and another substance or even the same substance in the matrix of the tablet, again to provide controlled release, for example, tablets comprising microencapsulated potassium chloride with a diuretic, for example, frusemide, in the matrix. The term "in the matrix of the tablet" means within the tablet but outside the microcapsule or coated form.

In addition to tablets for pharmaceutical (including veterinary) use, the tablets of the invention may comprise, for example, fertilizers, pesticides, disinfectants, or any other substance that is required *per se* in unit form or is required in unit form for adding to a determined amount of water or other solvent to produce a solution of known strength. The tablets of the invention are a form of preparation that is not only more convenient but also safer to handle.

Further examples of substances for which slow release is advantageous are trace additives for water supplies, nutritional and trace additives for fish ponds, and disinfection agents for swimming pools. Such substances may be microencapsulated or coated and tableted in accordance with the invention.

Microencapsulation or coating improves the stability of substances, and is particularly useful for preserving the activity of flavouring agents and vitamins, which are, accordingly, further suitable ingredients for the tablets of the invention.

The following Examples illustrate the invention.

Example 1

Tablets having the following composition were prepared:

	A	B	C	D
	mg	mg	mg	mg
KCl microcapsules	940	940	940	940
N-(2-Furfuryl)-4-chloro-5-sulphamoyl-anthranilic acid	-	-	-	20
Microcrystalline cellulose	94	94	94	94
Magnesium stearate	3	3	3	3
Amberlite IRP resin*	100	100	100	100
Carbopol 934	10	10	10	10
PEG 6000	94	47	188	47

The components were admixed thoroughly and compessed to tablets.

Tablets A to C, together with tablets having the same formulation except that they contained no PEG, were used to obtain the data presented in the accompanying drawing. Curve 1 shows the release from tablets containing no PEG, curves 2, 3 and 4 show the release from tablets corresponding to Examples B, A and C respectively.

*Amberlite IRP resin is the potassium salt of a cross-linked carboxylic acid cation exchange resin. It is used as a tablet disintegrant and it is unlikely that it either contributes to the potassium ions released or binds the released potassium ions. Amberlite is a Trade Mark.

Example 2

Tablets were prepared as described in Example 1A except that PEG 1000 was used instead of PEG 6000. The PEG 1000 was milled to a fine powder in the presence of 50 % solid CO_2 before use.

Example 3

Tablets were prepared as described in Example 2 except that PEG 35000 was used instead of PEG 1000

Example 4
Tablets were prepared as described in Example 2 except that instead of PEG 1000 there was used 50 % by weight of PEG 1000 and 50 % by weight of PEG 35000.

Example 5
Tablets were prepared as described in Example 1A and were then sintered for 1 hour at 70°C. The hardness of the tablets was increased by this treatment.

Example 6
Tablets were prepared as described in Example 1A and were then sugar coated in a coating pan using talc in syrup as the grossing coat and Tartrazine lake dispersed in syrup as the colour coating.

Example 7
Tablets were prepared as described in Example 1 and were then film coated by spraying an aqueous solution of hydroxypropylmethyl-cellulose on to the tablets in a coating pan.

Example 8
Tablets were prepared as described in Example 1A except that 20 mg of polyvinylpyrrolidone was used instead of the Carbopol 934.

Example 9
Tablets were prepared as described in Example 1A except that the microcrystalline cellulose was replaced by 94 mg of lactose.

Example 10
Tablets were prepared as described in Example 1A except that the Amberlite IRP resin was replaced by 100 mg starch.

Example 11
Tablets were prepared as described in Example 1A except that the Amberlite IRP resin was replaced by 40 mg Primogel (ultra amylopectin).

Example 12
Tablets having the following formula were prepared:

		mg
1.	KCl microcapsules	940
2.	Lactose	94
3.	Starch	100
4.	Polyvinyl pyrrolidone	20
5.	PEG 6000	94
6.	Magnesium stearate	3

Components 2, 3, 5 and 6 were granulated with component 4 dissolved in water. The granulation was carried out by wet massing and screening in a planetary mixer, by using a high speed mixer-granulator and by spray granulation. In each case, the resulting granules were dried, mixed with component 1, and compressed into tablets.

Example 13
Tablets having the formula given in Example 12 were prepared by mixing components 2, 3, 4, 5 and 6 and dry granulating the mixture by slugging on a tablet machine, and by means of a compactor. In each case, the resulting granules were crushed, passed through a screen having a 1 mm mesh size, mixed with the microcapsules of KCl, and compressed into tablets.

Example 14
Tablets were prepared as described in Example 1A and Example 9, in each case replacing the magnesium stearate by 3 mg of stearic acid.

WHAT WE CLAIM IS:-

1. A tablet (as hereinbefore defined) produced by compression which comprises a microencapsulated substance or a substance that has a brittle coating, and a water-soluble natural or synthetic wax having a melting point of at least 30°C in amount more than 2 % w/w and not more than 20 % w/w, calculated on the microcapsules or substance having a brittle coating.

2. A tablet as claimed in claim 1, wherein the wax has a melting point within the range of from 30 to 100°C.

3. A tablet as claimed in claim 1 or claim 2, wherein the wax is a polyethylene glycol.

4. A tablet as claimed in claim 1 or claim 2, wherein the wax is a stearate.

5. A tablet as claimed in claim 4, wherein the stearate is sodium stearate or polyoxyl 40 stearate.

6. A tablet as claimed in any one of claims 1 to 5, which comprises more than 3 % by weight of the wax.

7. A tablet as claimed in claim 6, which comprises more than 5 % by weight of the wax.

8. A tablet as claimed in any one of claims 1 to 7, which comprises not more than 10 % by weight of the wax.

9. A tablet as claimed in claim 8, which comprises from 5 to 10% by weight of the wax.

10. A tablet as claimed in any one of claims 1 to 9, wherein the coating substance used to form the microencapsulation or the brittle coating is an acrylic resin, ethylcellulose, nylon, glycerylmonostearate or beeswax.

11. A tablet as claimed in any one of claims 1 to 10, which also comprises one or more pharmaceutically suitable carriers in addition to the wax.

12. A tablet as claimed in claim 11, wherein the carrier(s) is or are selected from microcrystalline cellulose, lactose, starches and sugars.

13. A tablet as claimed in any one of claims 1 to 12, wherein the microencapsulated substance or substance having a brittle coating is a pharmacologically active substance, a fertilizer, a pesticide, a disinfectant, a nutritional or trace substance, or a flavouring agent.

14. A tablet as claimed in claim 13, wherein the substance is potassium chloride.

15. A tablet as claimed in any one of claims 1 to 12, which comprises one active substance in microencapsulated or coated form and the same or another substance in the matrix of the tablet or article.

16. A tablet as claimed in claim 15, wherein the substance in microencapsulated form is potassium chloride and a diuretic is present in the matrix.

17. A tablet as claimed in any one of claims 1 to 16, which has been sintered.

18. A tablet as claimed in claim 1, substantially as described in any one of the Examples herein.

19. A process for the production of a tablet as claimed in claim 1, which comprises admixing the microencapsulated substance or substance having a brittle coating and the wax and, if desired, one or more carriers, and bringing the mixture into tablet form or the other desired solid form; or applying a solution of the wax in an organic solvent to the micro-encapsulated substance or substance having a brittle coating, if desired, before or after admixture with one or more carriers, and bringing the treated substance and any carriers present into tablet form.

20. A process as claimed in claim 19, wherein the tablet or article is subjected to a post-treatment.

21. A process as claimed in claim 20, wherein the post-treatment is coating or lacquering.

22. A process as claimed in claim 21, wherein the post-treatment is sintering.

23. A process as claimed in claim 22, wherein the sintering is carried out at a temperature about 10°C above the melting point of the wax used.

24. A process as claimed in claim 19, carried out substantially as described in any one of the Examples herein.

25. A tablet as claimed in claim 1, whenever produced by a process as claimed in any one of claims 19 to 24.

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1 SHEET *This drawing is a reproduction of the Original on a reduced scale*